Efficacy, Safety, and Tolerability of AMT-101: A Gut Selective Oral IL-10 Fusion, in the Phase 2 FILLMORE Trial of Patients with Chronic Pouchitis

Vipul Jairath[1], Brian Bressler[2], Mark S. Silverberg[3], Li-Yin Lee[4], Kyler A. Lugo[4], Rafael Mayoral Monibas[4], Thamil Annamalai[4], J. Andrew Whitney[4], Emily Y. Weng[4], Bittoo Kanwar[4], Silvio Danese[5], Brian Feagan[1]

[1]Western University, London, Ontario, Canada; [2]University of British Columbia, Vancouver, Canada; [3]Mount Sinai Hospital, University of Toronto, Toronto, Canada
[4]Applied Molecular Transport Inc, South San Francisco, United States; [5]University Vita-Salute San Raffaele, Milan, Italy

BACKGROUND

Chronic Pouchitis: can occur in up to half of patients within 10 years of ileal pouch-anal anastomosis (IPAA) after proctocolectomy for ulcerative colitis (UC). There is a large unmet need for medical treatments.

AMT-101 -- An IL-10 Fusion Biologic: Oral & GI-selective biologic that combines rhIL-10 with a trafficking domain derived from the cholix protein (secreted by *Vibrio cholerae)*. Cholix utilizes active cellular machinery to rapidly move IL-10 through GI epithelium.

METHODS

- **FILLMORE Trial:** A Phase 2, randomized double-blind, parallel-group, 2 active-arm trial of the combined phase 2/3 trial in adults (18-75 years) with a prior history of UC with proctocolectomy and subsequent IPAA, who presented with chronic or recurrent pouchitis.
- **Conducted in US, Canada, and Western Europe.** Approximately 20 patients were planned to be randomized 1:1 to either 3 mg or 10 mg AMT-101 doses administered once daily, orally, for 12 weeks.
- **Key efficacy endpoints:** 1) Proportion of patients with symptomatic improvement, as measured by stool frequency response, and 2) Proportion of patients with histologic healing, as measured by Geboes scores. Histology and endoscopy were centrally read.

DISPOSITION

- A total of 45 patients were screened and 22 participants were randomized to treatment with AMT-101 3 mg (N=10) or AMT-101 10 mg (N=12).
- Overall, 72.7% of patients completed the study. Completers were well balanced between the two groups.

BASELINE CHARACTERISTICS

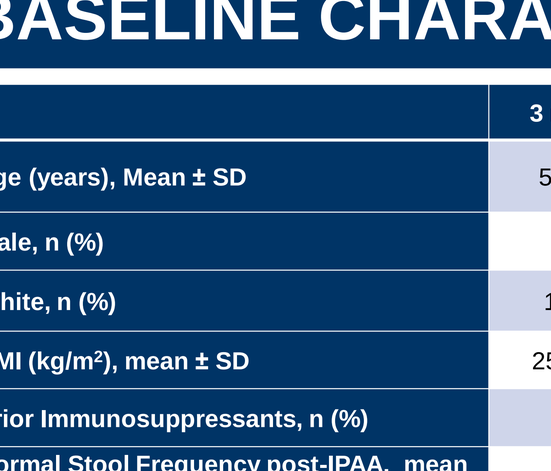
	3 mg (N=10)	10 mg (N=12)	Total (N=22)
Age (years), Mean ± SD	54.9 ± 13.4	47.7 ± 14.6	51.0 ± 14.2
Male, n (%)	7 (70.0)	9 (75.0)	16 (72.7)
White, n (%)	10 (100.0)	9 (75.0)	19 (86.4)
BMI (kg/m^2), mean ± SD	25.78 ± 2.29	25.63 ± 4.41	25.70 ± 3.53
Prior Immunosuppressants, n (%)	5 (50.0)	5 (41.7)	10 (45.5)
Normal Stool Frequency post-IPAA, mean ± SD	7.9 ± 4.4	7.4 ± 3.6	7.6 ± 3.9
History of Pouchitis (years), Mean ± SD	4.07 ± 2.90	5.34 ± 5.63	4.76 ± 4.54
3 - Day Average Stool Frequency Count, mean ± SD	13.2 ± 3.6	13.5 ± 5.3	13.4 ± 4.5
Geboes Scores, median (Q1, Q3)	5.2 (3.2, 5.3)	4.2 (3.2, 5.2)	5.1 (3.2, 5.2)

BMI = body mass index; SD = standard deviation

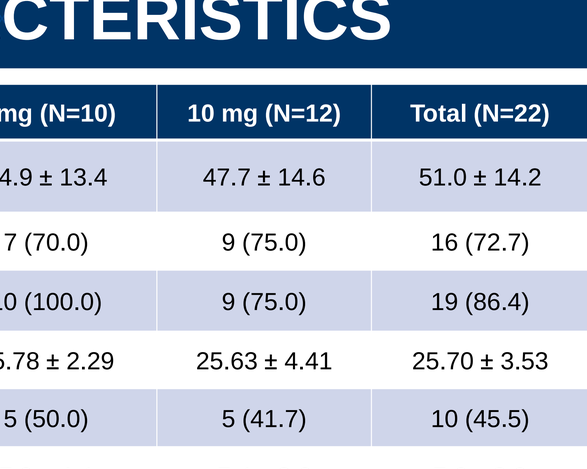
STOOL FREQUENCY

- Rapid stool frequency response was observed as early as Week 2 and was maintained throughout treatment and safety follow-up

Stool Frequency Response (%) at Week 12



Stool Frequency Response (%) by Visit

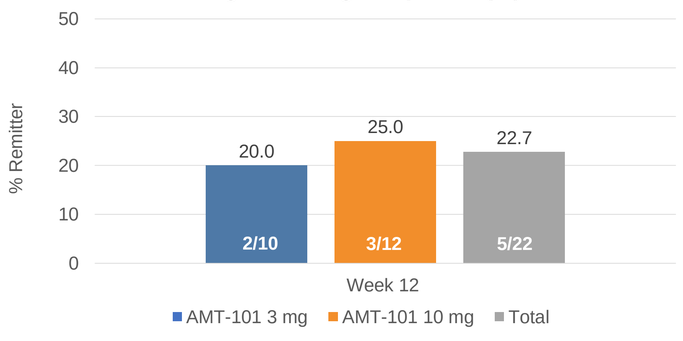


Stool Frequency Response was defined as a reduction of ≥ 3 stools AND ≥ 30% reduction in number of stools from baseline

HISTOLOGY

- Intestinal biopsies were collected from ileal pouch at Baseline and Week 12
- Overall, 22.7% (5/22) of participants achieved histological healing response

Histologic Healing Response (%) at Week 12



Histologic Healing Response was defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue (Geboes score ≤ 3.1)

SAFETY

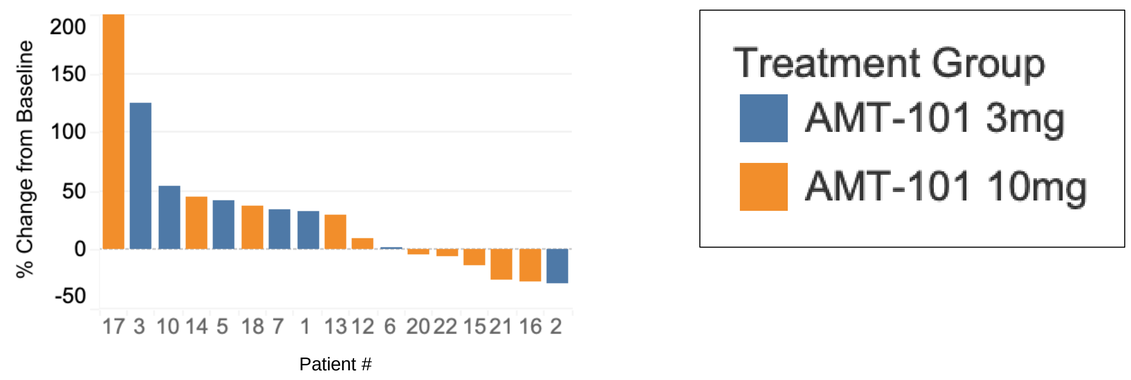
	3 mg (N=10)	10 mg (N=12)	Total (N=22)
Total number of TEAEs	21	25	46
Number of participants with at least one:			
TEAE, n (%)	7 (70.0)	9 (75.0)	16 (72.7)
Serious TEAE, n (%)	0 (0.0)	1 (8.3)[b]	1 (4.5)
Treatment-related TEAE, n (%)	2 (20.0)[a]	4 (33.3)[c]	6 (27.3)
TEAE leading to study discontinuation, n (%)	0 (0.0)	1 (8.3)[b]	1 (4.5)
TEAE leading to treatment discontinuation, n (%)	0 (0.0)	1 (8.3)[b]	1 (4.5)
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

TEAE = treatment-emergent adverse event; [a]Abdominal pain; [b] Cytomegalovirus infection;
[c]Pharyngitis, lymphopenia, haematocrit decreased, neutrophil count increased, appetite increased, cough, dry skin

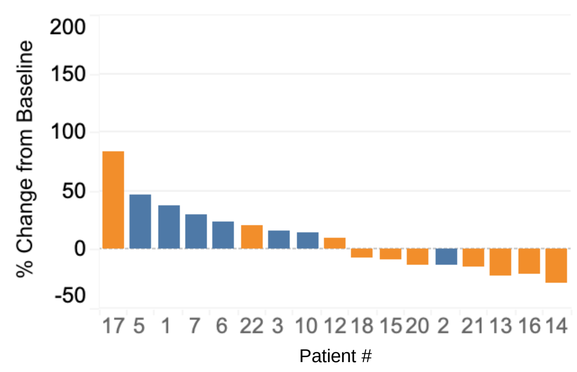
PK/PD RESULTS

- There was no systemic AMT-101 PK (by design) nor anti-drug antibodies detected. Translational analysis revealed IL-10 biological responses in both arms.
- In tissue, IHC results showed increases to anti-inflammatory FOXP3+ (Tregs) and CD163+ (M2-macrophages) cells in the lamina propria. Fecal microbiome results showed increases in overall diversity & decreased Proteobacteria abundances (10 mg).
- Biopsy RNASeq analysis showed improvement in gene families related to intestinal disease pathogenesis. Positive clinical responders showed increased absorption & transport pathways and decreased pro-inflammatory genes.

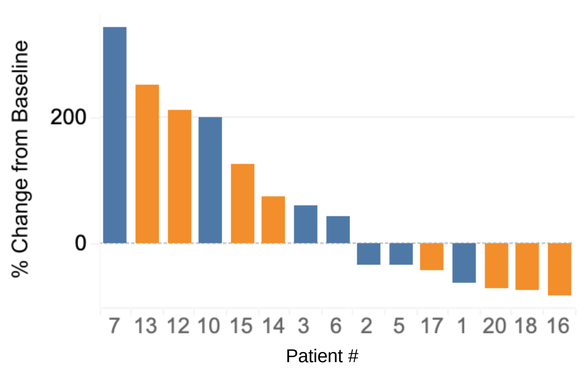
Biopsy IHC -- FOXP3+ Cells



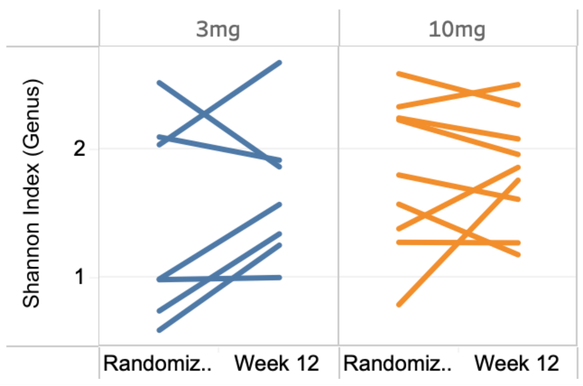
Biopsy IHC -- CD163+ Cells



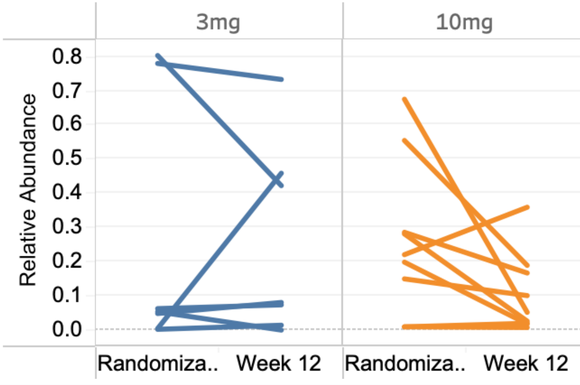
Biopsy pSTAT3 / STAT3 Ratio



Fecal Microbiome Diversity



Proteobacteria (Pseudomonadota)



CONCLUSIONS

- AMT-101 3 mg and 10 mg appeared to be safe and generally well tolerated. Both doses showed similar (not dose-proportional) positive efficacy results at Week 12, as demonstrated by stool frequency response and histologic healing.
- PK and translational data confirmed AMT-101's gut-restricted profile over the 12-week treatment with tissue-level PD effects and no systemic exposure.
- An independent Data Monitoring Committee has recommended AMT-101 advances into phase 3.

DISCLOSURES

- VJ has received has received consulting/advisory board fees from AbbVie, Alimentiv Inc, Arena pharmaceuticals, Asahi Kasei Pharma, Asieris, Astra Zeneca, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Metacrine, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Prometheus, Reistone Biopharma, Roche, Sandoz, Second Genome, Sorriso pharmaceuticals, Takeda, Teva, Topivert, Ventyx, Vividion; speaker's fees from, Abbvie, Ferring, Bristol Myers Squibb, Galapagos, Janssen Pfizer Shire, Takeda, Fresenius Kabi
- BB: Advisor/Speaker: Ferring, Janssen, Abbvie, Takeda, Pfizer, Novartis, BMS, Merck, Sandoz, Organon. Advisor: Alimentiv, Gilead, Iterative Scopes, AMT, Celgene, Microbiome Insights, Merck, Amgen, Pendopharm, Genentech, BMS, Allergan, Protagonist, Fresenius Kabi, Mylan, Viatris, Bausch Health, Celltrion Healthcare, Jamp Pharma, Eupraxia. Research support: Janssen, Abbvie, GSK, BMS, Amgen, Genentech, Merck, BI, Qu Biologic. Stock Options: Qu Biologic
- MS: Speaker, Advisory Board and Consulting Fees received from: Abbvie, Janssen, Takeda, Pfizer
- LL, KL, RMM, TA, JAW, EW, and BK are all employees of AMT and own stock in the company
- This presentation concerns product candidates that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). Those product candidates are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated

APPLIED | MOLECULAR | TRANSPORT